International Journal of Immunology
2025, Vol. 13, No. 4, pp. 90–95
https://doi.org/10.11648/j.iji.20251304.12

Research Article

Kappa Free Light Chain Index as a Diagnostic Biomarker in Multiple Sclerosis: Validation in an Argentinian Cohort and Cut off Proposal

Silvia Graciela Ramos[1, *], Andrés Maria Villa[2, 3], Analisa Manin[2, 3], Viviana Novoa[1], Claudio Aranda[4]

[1]Immunology Laboratory, General Acute Care Hospital Dr. Carlos G. Durand, Buenos Aires, Argentina
[2]Neurology Division. General Acute Care Hospital Dr. José María Ramos Mejía, Buenos Aires, Argentina
[3]Argentine Center for Neuroimmunology (CADENI), University of Buenos Aires, Buenos Aires, Argentina
[4]Central Laboratory Division, General Acute Care Hospital Dr. Carlos G. Durand, Buenos Aires, Argentina

Abstract

Background: Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS). Cerebrospinal fluid (CSF) analysis, including oligoclonal bands (OCB) and the IgG index, is central to MS diagnosis but presents technical and interpretative limitations. The kappa free light chain (κFLC) index has emerged as a promising biomarker of intrathecal immunoglobulin synthesis. Objective: To evaluate the diagnostic performance of the κFLC index in MS, determine an optimal cutoff value, and compare its accuracy with OCB detection and the IgG index. Methods: We conducted a retrospective study including 176 patients evaluated at the Neuroimmunology Laboratory of Buenos Aires, Argentina. Patients were classified into four groups: MS (n = 106), neuromyelitis optica spectrum disorders (NMOSD, n = 15), other inflammatory CNS disorders of autoimmune or infectious origin (ICNSDAI, n = 41), and paraneoplastic neurological syndromes (PNS, n = 14). κFLC, IgG, and albumin concentrations were measured in paired CSF and serum samples. The κFLC index was calculated and compared with OCB and IgG index results. Diagnostic performance was assessed using receiver operating characteristic (ROC) curve analysis. Results: The κFLC index was significantly higher in MS patients (median: 85; IQR: 30–305) compared with NMOSD (3.37), ICNSDAI (1.62), and PNS (1.96) groups ($p < 0.0001$). A κFLC index cutoff of 15 demonstrated 92% sensitivity and 83% specificity, with an area under the ROC curve of 0.952. The κFLC index correlated with the IgG index ($\rho = 0.587$, $p < 0.0001$) and OCB positivity ($\rho = 0.586$, $p < 0.0001$). κFLC index values ≥100 were observed almost exclusively in MS, with one exception in a patient with acute HSV-1 encephalitis. Conclusion: The κFLC index is a sensitive and reliable biomarker for intrathecal immunoglobulin synthesis in MS, offering advantages of automation, rapid processing, and objective quantification. External validation in independent cohorts is required before routine clinical implementation.

Keywords

Multiple Sclerosis, Cerebrospinal Fluid, Kappa Free Light Chains, Oligoclonal Bands, Intrathecal Immunoglobulin Synthesis, Biomarkers

*Corresponding author: Sgramos58@hotmail.com (Silvia Graciela Ramos)

Received: 24 November 2025; **Accepted:** 6 December 2025; **Published:** 29 December 2025

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS), diagnosed through a combination of clinical assessment, neuroimaging, and cerebrospinal fluid (CSF) analysis [1]. Evidence of intrathecal immunoglobulin G (IgG) synthesis—most commonly assessed by oligoclonal bands (OCB) or the IgG index—represents a cornerstone of MS diagnosis and contributes to the exclusion of alternative neurological disorders [2].

OCB are detected in more than 90% of patients with MS and are considered a highly sensitive marker of chronic intrathecal IgG production. Their inclusion in the 2017 McDonald criteria highlights their importance, particularly for demonstrating dissemination in time in patients with clinically isolated syndrome (CIS). However, OCB analysis is limited by cost, technical complexity, and inter-laboratory variability. The IgG index, while more accessible, shows inferior sensitivity and specificity compared with OCB.

In recent years, quantification of free kappa light chains (κFLC) in CSF and serum has emerged as a promising alternative biomarker of intrathecal immunoglobulin synthesis. The κFLC index, calculated by normalizing CSF/serum κFLC ratios to albumin concentrations, has demonstrated diagnostic performance comparable to OCB in several studies. Additionally, it offers practical advantages, including automation, rapid turnaround, and standardized quantification, making it attractive for routine clinical use [3-5].

Data regarding κFLC index performance in Latin American populations remain limited. Therefore, this study aimed to evaluate the diagnostic utility of the κFLC index in a local cohort from Buenos Aires, Argentina, determine an optimal cutoff value, and assess its performance relative to OCB detection and the IgG index.

2. Materials and Methods

2.1. Study Design and Population

This retrospective observational study was conducted at the Neuroimmunology Laboratory within the public hospital network of the Autonomous City of Buenos Aires, Argentina. Consecutive paired CSF and serum samples obtained for diagnostic purposes were analyzed.

Patients were classified into four diagnostic groups:

1) Multiple sclerosis (MS), based on the 2017 McDonald criteria.
2) Neuromyelitis optica spectrum disorders (NMOSD), according to the 2015 IPND consensus criteria.
3) Other inflammatory CNS disorders of autoimmune or infectious origin (ICNSDAI).
4) Paraneoplastic neurological syndromes (PNS).

The study was approved by the local Institutional Review Board. Due to the retrospective design and anonymized data analysis, the requirement for informed consent was waived.

2.2. Diagnostic Protocol

All included patients underwent a standardized diagnostic work-up comprising:

1) Oligoclonal band (OCB) detection via isoelectric focusing and immunofixation.
2) Quantification of albumin, IgG, and free kappa light chains (κFLC) in CSF and serum.
3) Calculation of IgG index and κFLC index.

2.3. Laboratory Procedures

2.3.1. Oligoclonal Band Detection

OCB analysis was performed using isoelectric focusing (IEF) on agarose gel with the semi-automated Hydrasys® system (SEBIA, France). Samples were standardized to an IgG concentration of 20 mg/L and loaded in parallel lanes for CSF and serum. Immunofixation was carried out with peroxidase-conjugated anti-IgG antiserum, enhancing detection sensitivity 100-fold. Gels were visually interpreted by two experienced evaluators. OCB positivity was defined as the presence of at least two bands in CSF not found in the paired serum sample.

OCB electrophoretic patterns were classified into five categories:

1) No bands in CSF or serum
2) Bands in CSF only (indicative of intrathecal synthesis)
3) Bands in both fluids, but more in CSF
4) Identical patterns in CSF and serum
5) Monoclonal pattern in both samples

2.3.2. Biochemical Quantification

Concentrations of albumin, IgG, and κFLC in CSF and serum were measured using immunoturbidimetric assays on the SpaPlus® analyzer (The Binding Site Group Ltd., UK). All samples were handled under standardized preanalytical conditions.

2.3.3. Index Calculations

Intrathecal synthesis was assessed using the following formulas:

1) *IgG index* = QIgG / QAlb
2) *κFLC index* = QκFLC / QAlb

Where:

1) QIgG = CSF IgG / serum IgG
2) QκFLC = CSF κFLC / serum κFLC
3) QAlb = CSF albumin / serum albumin

3. Statistical Analysis

Non-parametric methods were used due to non-normal data distribution. Group comparisons were performed using Kruskal–Wallis and Mann–Whitney U tests with Bonferroni correction. Correlations were assessed using Spearman's coefficient. Diagnostic accuracy was evaluated using ROC

curve analysis. Agreement between methods was tested with McNemar's test.

4. Results

A total of 176 patients were included in the study, of whom 60.8% were women. The mean age of the cohort was 42 ± 12 years. Based on clinical and laboratory criteria, patients were categorized into four groups: 106 with multiple sclerosis (MS), 15 with neuromyelitis optica spectrum disorders (NMOSD), 41 with other inflammatory CNS disorders of autoimmune (20 neuropsychiatric systemic lupus erythematosus, 10 Sjogren's syndrome) and 11 infectious origin (ICNSDAI), and 14 with paraneoplastic neurological syndromes (PNS). The age difference between the MS and PNS groups may introduce confounding variables, as age is a known factor in some CNS disorders. Future studies should control for age to ensure that observed differences are not influenced by demographic factors. Demographic data for each group are summarized in Table 1.

Table 1. Demographic characteristics of study groups.

Group	Sex (F/M)	Age (mean ± SD)
MS (n=106)	60% / 40%	38 ± 15 years
NMOSD (n=15)	65% / 35%	43 ± 17 years
ICNSDAI (n=41)	63% / 37%	39 ± 13 years
PNS (n=14)	58% / 42%	48 ± 10 years

4.1. κFLC and Index Values Across Groups

Due to non-normal distribution of κFLC values in CSF and their corresponding indices (confirmed by Kolmogorov-Smirnov and Shapiro-Wilk tests), median values and interquartile ranges (IQR) were calculated. The MS group demonstrated markedly elevated κFLC index values compared to all control groups. Biochemical markers are shown in Table 2.

Table 2. Comparison of Biomarkers Across Diagnostic Groups.

Group	κFLC CSF (mg/dL)	κFLC Index	IgG Index	OCB Type 2 Positivity
MS	0.53 [0.07–1.03]	85.0 [30–305]	1.29 [0.63–1.95]	106/106 (100%)
NMOSD	0.10 [0.017–0.13]	3.37 [1.95–7.05]	0.57 [0.35–0.80]	0/15 (0%)
ICNSDAI	0.16 [0.10–0.56]	1.62 [0.99–2.27]	0.56 [0.38–0.75]	3/41 (7%)
PNS	0.15 [0.10–0.20]	1.96 [1.13–3.56]	0.58 [0.40–0.70]	1/14 (7%)

Cutoff for κFLC Index: >15 (proposed in this study as optimal threshold for MS diagnosis)
Cutoff for IgG Index: >0.7 (commonly used in clinical practice)
OCB Type 2 positivity: Defined as ≥2 bands in CSF absent in serum

Statistical comparison using the Kruskal-Wallis test revealed significant differences in κFLC CSF values and κFLC index values across the four diagnostic groups ($p < 0.0001$). Pairwise analysis with the Mann-Whitney U test were performed, with Bonferroni correction applied to adjust for multiple comparisons. After correction, all pairwise differences remained statistically significant ($p < 0.05$) by the number of comparisons. Statistical comparison using the Kruskal-Wallis test revealed significant differences in κFLC CSF values and κFLC index values across the four diagnostic groups ($p < 0.0001$).

4.2. κFLC Index vs. OCB and IgG Index

The κFLC index was significantly higher in OCB-positive patients compared to OCB-negative patients (71 ± 56 vs. 1.25 ± 0.93; $p < 0.0001$). Positive correlations were observed between the κFLC index and both the IgG index (Spearman's $\rho = 0.587$, $p < 0.0001$) and the presence of type 2 OCB ($\rho = 0.586$, $p < 0.0001$), indicating concordance between these markers of intrathecal synthesis.

4.3. Diagnostic Performance of the κFLC Index

The optimal cutoff value for the κFLC index was determined using receiver operating characteristic (ROC) curve analysis, which demonstrated an area under the curve (AUC) of 0.952 (95% CI: 0.910–0.968), indicating excellent diagnostic performance. To establish the most effective threshold for distinguishing MS from non-MS cases, we applied the Youden Index (J = sensitivity + specificity − 1), which identifies the point on the ROC curve that maximizes overall diagnostic accuracy. This analysis yielded an optimal κFLC index cutoff of 15, providing a sensitivity of 92% and specificity of 83%. This threshold balances false-positive and false-negative rates, making it clinically practical and suitable for implementation in routine diagnostics. In comparison, the IgG index showed an AUC of 0.781 (95% CI: 0.754–0.851), with 70% sensitivity and 69% specificity.

Notably, κFLC index performance was statistically comparable to that of OCB detection (OCB sensitivity: 95%, specificity: 91%), with McNemar's test showing no significant difference (p = 0.053) Table 3.

Table 3. Diagnostic accuracy.

	κFLC Index	OCB	IgG Index
AUC	0.952 [95% CI 0,910-0,968]	0.98 [95% CI 0,935-0,99]	0.781[95% CI 0,753-0,851]
Sensitivity	92%	95%	70%
Specificity	83%	91%	69%

4.4. κFLC Index Distribution

High κFLC index values (≥100) were exclusively observed in MS patients, with one exception: a patient diagnosed with acute herpes simplex virus type 1 (HSV-1) encephalitis. No other control patients exhibited similarly elevated levels, reinforcing the potential specificity of high κFLC index values for MS.

5. Discussion

This study confirms that the kappa free light chain (κFLC) index in cerebrospinal fluid (CSF) is a sensitive and specific biomarker of intrathecal immunoglobulin synthesis in multiple sclerosis (MS). Our findings demonstrate that κFLC index values were significantly elevated in MS patients compared to all control groups, supporting its diagnostic value and reinforcing its potential as a complementary marker, especially in cases where traditional methods are negative or inconclusive. While the diagnostic utility of the κFLC index has been established in previous studies, this research provides the first validation in an Argentinian cohort, offering new insight into its performance in a Latin American context. Additionally, the proposed cutoff value of 15 could provide a clinically useful threshold for diagnosing MS in routine practice.

5.1. Diagnostic Value of the κFLC Index

The κFLC index showed excellent diagnostic accuracy (AUC 0.952), outperforming the IgG index and demonstrating sensitivity and specificity comparable to oligoclonal band (OCB) detection, which remains the current gold standard for identifying intrathecal IgG synthesis. The correlations with both the IgG index and type 2 OCBs further support the κFLC index as a reliable indicator of central nervous system-restricted immune activity.

Importantly, κFLC index values ≥100 was observed exclusively in MS patients, with one exception—a patient diagnosed with acute herpes simplex virus type 1 (HSV-1) encephalitis. This suggests that κFLC ≥100 may be highly suggestive of MS but should not be regarded as exclusive to it, particularly in cases of acute viral encephalitis. This suggests that markedly elevated κFLC index values may be highly specific for MS in the appropriate clinical context, although caution is warranted due to possible overlap with acute viral encephalitis.

5.2. Comparison with Previous Studies

Our results are consistent with prior research validating the κFLC index as a robust diagnostic marker for MS [6, 7]. Similar to those studies, we found that the κFLC index effectively distinguishes MS from other inflammatory neurological disorders, even in cases where OCB detection fails. As a quantitative and objective measure, the κFLC index addresses many limitations associated with OCB analysis, such as subjectivity in interpretation and variability across laboratories [8-11].

5.3. Clinical Utility and Practical Advantages

Beyond its diagnostic accuracy, the κFLC index presents a practical, objective, and rapid alternative for assessing intrathecal synthesis. In resource-limited settings or where

access to isoelectric focusing is unavailable, it may enable more timely and standardized MS diagnosis. Its potential for automated implementation could support future integration into diagnostic algorithms, provided that external validation and cut-off standardization are achieved [12-14].

5.4. Limitations and Future Directions

This study has several limitations. First, its retrospective design may introduce selection bias and does not allow for assessment of the prognostic utility of the κFLC index over time. Second, the sample sizes of non-MS control groups—particularly NMOSD (n=15) and paraneoplastic syndromes (n=14)—were relatively small, limiting statistical power and generalizability. Although significant differences were observed between groups, these findings should be confirmed in larger and more diverse cohorts.

Furthermore, this study did not include patients with clinically isolated syndrome (CIS) or those with suspected early-stage MS, where the κFLC index may have the greatest clinical utility. The ability of the κFLC index to predict conversion to MS in this population remains an important area for future investigation. In addition, the proposed cut-off value (κFLC index ≥15) was not externally validated in an independent cohort, which is essential for assessing its robustness across different populations and settings.

Finally, although the κFLC index demonstrated diagnostic performance similar to OCBs, it has not yet been formally incorporated into the 2017 McDonald criteria. Multicenter prospective studies, including longitudinal clinical and imaging follow-up, are needed to evaluate its prognostic value and reproducibility across laboratories.

Lack of standardized κFLC reference ranges in Latin American populations remains a barrier for broader clinical adoption.

6. Conclusion

The κFLC index is a reliable, quantitative, and efficient biomarker for detecting intrathecal immunoglobulin synthesis in MS. Its strong diagnostic performance and practical advantages support its potential role as a complementary diagnostic tool. Nevertheless, external validation in independent and diverse populations is required before routine clinical implementation [15, 16].

Abbreviations

CNS	Central Nervous System
CSF	Cerebrospinal Fluid
IgG	Immunoglobulin G
OCB	Oligoclonal Bands
κFLC	Kappa Free Light Chains
MS	Multiple Sclerosis
NMOSD	Neuromyelitis Optica Spectrum Disorders
ICNSDAI	Inflammatory CNS Disorders of Auto immune or Infectious Origin
PNS	Paraneoplastic Neurological Syndromes
AUC	Area Under the Curve
ROC	Receiver Operating Characteristic
SPSS	Statistical Package for the Social Sciences
IEF	Isoelectric Focusing
IPND	International Panel on Neuromyelitis Optica
CIS	Clinically Isolated Syndrome

Conflicts of Interest

The authors declare no conflicts of interest.

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